Original Article

Hepatotoxicity in Anti TB Drugs

Drug Induced Hepatotoxicity and the Risk Factors for Liver Injury During Treatment of Pulmonary Tuberculosis

Jeando Khan Daidano, Mujahid Chandio, Mukhtiar Abro and Rafique Ahmed Memon

ABSTRACT

Objective: To determine the frequency of drug induced hepatitis due to ATT the presentation of the patient during treatment of pulmonary tuberculosis and the risk factors.

Study Design: Retrospective / Descriptive study.

Place and Duration of Study: This study was conducted at the Department of Medicine at PMCH Nawabshah from August 2015 to August 2017.

Materials and Methods: 100 patients were selected after inclusion criteria on a preformed Performa. Patients selected for this study were from all age groups and gender, diagnosis was made by history, clinical examination of the patient and investigations. All patients were on ATT in pulmonary tuberculosis.

Results: 100 patients participated for this study. 61 were males and 39 were females. Jaundice was present in all the patients, hepatomegaly was noted in 68 patients, Serum Bilirubin ranged 4.90 to 16 mean10.18 , SGPT ranged 279 to 432 mean 329.31, PT ranged 17-26 mean 21.16. Pyrazinamide was found more hepatotoxic than isoniazid and rifampicin after weekly trial after normalization of SGPT and Bilirubin. Statical analysis was done using software SPSS 15 version.

Conclusion: Due to drug induced hepatitis treatment failure or drug resistant in pulmonary tuberculosis is a big problem. Liver function test during treatment is essential especially in risk factors. Awareness of the patients and their relatives about treatment of pulmonary tuberculosis and drug induced hepatitis is necessary to reduce complications and mortality.

Key Words: Hepatoxicity ATT Pulmonary Tuberculosis

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INTRODUCTION

Incidence of tuberculosis was at increased level in 2003, now there is a slow decline. 9 millions new cases are reported every year and death ratio estimated to be 1.5 million per year.[1] Pulmonary tuberculosis is major problem worldwide.[1] First line anti tuberculosis drugs are Rifampicin, Isoniazid, Ethambutol and Pyrazinamide initially two months followed by four months of Rifampicin, Isoniazid or Ethambutol.[2] Three drugs Isoniazid, Pyrazinamide and Rifampicin are metabolized by liver. Incidence of drug induced liver injury by ATT is reported in 2-28%. Pathogenesis and biochemical mechanism of these ATT drugs to cause liver injury is not clear. During treatment of tuberculosis therapeutic drug monitoring is helpful to check drug resonse to treatment, drug drug interaction and drug resistance TB.

Department of Medicine-PUMHS, Nawabshah.

Correspondence: Dr. Jeando Khan Daidano, Assistant Professor of Medicine-PUMHS, Nawabshah.
Contact No: 0345-3643713
Email: jeandokhan@ymail.com

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There are chances of treatment failure if one of the drug is terminated. Risk factors for anti-TB drug induced hepatitis can be due to acetylators of of isoniazid metabolites, may be a cause of hepatotoxicity.[3] Pyrazinamide is more hepatotoxic than other first line anti TB drugs. Pyrazinamide induced hepatotoxicity is decreased due to changing in standard dose. Pyrazinamide is thought to be the most common drug causing anti TB drug induced hepatitis.[4] Complication include co infection with HCV, HBV, HIV and CLD. Advanced age, malnutrition, female sex and slow acetylators increase risk of hepatotoxicity.[5] Roussel Uclaf Causality Assessment Methos (RUCAM) score is used in cases of suspected drug induced liver injury. Patients who are on isoniazid monotherapy for latent TB transaminitis with ATT may represent hepatic adaptation and occurs in 20% of patients. Criteria based on ALT, ALP and Bilirubin to guide cessation of ATT were used by drug induced liver injury expert working group and DILIGEN study.[6] ALT >5 x ULN or if the patient is icteric than recommendation for treatment cessation or if ALT is 3-5 x ULN and the patient has nausea, vomiting, anorexia, jaundice and abdominal pain than cessation of treatment recommended by ATS.[7] Patients with drug induced liver injury were managed according to local guidelines. If ALT was 3-5 xULN with symptoms or >5 x ULN without symptoms.

ATT was changed and non-hepatotoxic regimen Ethambutol plus Amikacin is prescribed stopping Pyrazinamide, Rifampicin and Isoniazid.[7]

MATERIALS AND METHODS

This retrospective descriptive study was conducted in the department of medicine PMCH Nawabshah. 100 patients were enrolled for this study on a preformed proforma with questionnaire, informed consent was taken from all the patients who participated for the study, all patents were on ATT due to pulmonary tuberculosis. History was taken from all the patients along with general physical examination and systemic examination. All patients were investigated for SGPT, serum BILIRUBIN,PT, HBsAg, anti HCV, HIV, Urea, RBS and Ultrasound of abdomen.

Inclusion criteria:

Jaundice positive
History of ATT
Increased Bilirubin
Raised SGPT

Exclusion criteria:

Jaundice negative
No history of ATT
Normal Bilirubin
Normal SGPT

RESULTS

All patients presented with jaundice, all were on ATT due to pulmonary tuberculosis. Males were 59 and females were 41. Age ranged from 43 to 69 years mean 58.28. 32 patients presented with vomiting, 49 patients presented with pain in right hypochondrium and epigastrium. Itching was noted in 23 patients, loss of appetite in all patients, dark colour urine noticed by 84 patients. On examination jaundice was positive in all the patients, hepatomegaly was present in 68 patients.

Table No.1: Descriptive Statistics

Variables	N	Min.	Max.	Mean	Std. Deviat.
Age	100	43.00	69.00	58.2800	5.19922
Sex	100	1.00	2.00	1.3900	0.49021
Education	100	1.00	3.00	1.3500	0.57516
Occupation	100	1.00	3.00	1.6100	0.68009
Bilirubin	100	4.90	16	10.1822	2.78840
SGPT	100	279.00	432.00	329.3100	28.56101
PT	100	17.00	26.00	21.1600	2.25953
RBS	100	92.00	197.00	151.0100	22.92918
Urea	100	23.00	41.00	33.2100	4.40912
Valid N(listwise)	100				

Table No.2: Paired Correlations

Variables in Pairs	N	Correlation	Significant
Pair 1 Age & Sex	100	-0.297	0.003
Pair 2 Bilirubin & SGPT	100	0.352	0.000
Pair3 Education & Occupation	100	-0.087	0.392
Pair 4 PT & SGPT	100	0.349	0.000

Table No.3: ANOVA

Variables	Sum of Squares	df	Mean Square	F	Significant
Age Between Groups	112.329	2	56.164	2.125	0.125
Within Groups	2563.831	97	26.431		
Total	2676.160	99			
Sex Between Groups	4.507	2	2.254	11.336	0.000
Within Groups	19.283	97	0.199		
Total	23.790	99			
Occupation Between Groups	12.907	2	6.454	19.037	0.000
Within Groups	32.883	97	0.339		
Total	45.790	99			
Bilirubin Between Groups	17.770	2	8.885	1.146	0.322
Within Groups	751.975	97	7.752		
Total	769.545	99			
SGPT Between Groups	84.259	2	42.129	0.51	0.951
Within Groups	80673.131	97	831.682		
Total	80757.390	99			
PT Between Groups	71.414	2	35.707	7.980	0.001
Within Groups	434.026	97	4.474		
Total	505.440	99			
RBS Between Groups	8309.859	2	4154.929	9.214	0.000
Within Groups	43739.131	97	450.919		
Total	52048.990	99			
Urea Between Groups	97.687	2	48.844	2.593	0.080
Within Groups	1826.903	97	18.834		
Total	1924.590	99			

Serum Biirubin ranged 4.9 to 16, SGPT ranged 279 to 432, PT ranged 17 to 26. ATT was stopped and liver non toxic drugs ethambutol and amikicin were continued. Instructions to patients were given about treatment of jaundice and tuberculosis, investigated weekly for LFT.After normalization of SGPT and Bilirubin, and patient become symptom free, trial of isoniazid and later rifampicin were given, it was observed that out of 100 patients only in 3 patients hepatitis reoccur due to isoniazid, 7 patients with rifampicin and trial of pyrazinamide was not given due to its toxic effect more than isoniazid and rifampicin. Rifampicin and isoniazid reintroduced in the regimen in all the patients who were not affected by rifampicin and isoniazid. In statical analysis male denoted by 1 and female by 2, education uneducated by 1, primary by 2, middle by 3, occupation farmer by 1, housewife 2, self employed by 3. Statical analysis analysed using software 15 version.

DISCUSSION

Tuberculosis is a major disease worldwide. First line ATT are rifampicin, isoniazid, pyrazinamide and ethambutol, hepatitis due to rifampicin, isoniazid and pyrazinamide is big problem of treatment failure. Risk factors for ATT induced hepatitis are female gender, old age, alcoholism, HIV infection and underlying liver disease studies done previously.[8] Few patients presented with drug induced hepatitis in first 2 weeks of drug intake,87% patients presented in first 2 months after ATT.[9] Drug induced hepatitis vary in different countries ranging 1-10% in developing countries ratio is 8-10% , in western countries ratio is 1% to 3.3%.[10] In developing countries risk factors noted are old age, past history of jaundice, CLD, indiscriminate use of drugs, viral hepatitis B, viral hepatitis C intestinal parasite infestation, alcoholism, female gender, low body mass index, HIV,[11] acetylator status, hypoalbuminemia and malnutrition. It was observed in one study that malnutrition and disseminated TB were independent predictors in the development of drug induced hepatitis in the TB patients with HIV infection.[11] Rifampicin and isoniazid are the main drugs in TB, mechanism of action is separate, direct toxicity from isoniazid metabolites cause hepatocyte death and elevation of tranaminase, histopathological was similar to viral hepatitis.[12] Metabolism of rifampicin is through liver and excretion is through bile duct, rifampicin cause drug interaction with other drugs like warfarin through enterohepatic circulation.[13] Rifampicin in combination with other anti tuberculosis drugs increase hepatotoxicity 1.6-2.55 % in adults.[13] Pyrazinamide associated with increased in incidence of hepatotoxicity. Ederly patients are at increased risk of hepatitis due to comorbid disease and additional drugs compared with young population.[14] There was increased risk of hepatitis in age >40 years in a study.[14] Female gender was at increased risk of hepatitis due to ATT. The pathogenesis and biochemical mechanism of ATT to cause hepatitis is not clear. Hepatitis associated with pyrazinamide in high dose >40 mg/kg,[15] in pharmacodynamic and phrmakokinetic studies pyrazinamide in high doses is effective than the current recommended doses.[15] In studies rifampicin in high doses is effective. Low serum level of isoniazid and rifampicin associated with low therapeutic efficacy and high treatment failure.[16] Limited data are available if physician increase the dose of ATT, may lead to hepatitis in tuberculosis patients. Tuberculosis in the USA has increased due to many reasons, none of those are more important than HIV. HIV may predispose to the development of drug induced liver injury with ATT. HCV and HIV are independent additive risk for the drug induced liver injury. Alcohol and antiretroviral drugs with ATT increase hepatotoxicity. Chronic alcohol abuse is important risk for the hepatotoxicity with ATT.[17] Rifabutin a rfamycin derivative is more effective in the TB treatment and less hepatotoxic than rifampicin. An immune related mechanism of drug induced hepatitis exist for isoniazid and rifampicin.[18] ALT elevated 3 times ULN with symptoms or ALT level elevated of 5 times ULN, stop the ATT, give non hepatotoxic ethambutol, flouroquinolone or cycloserine could be considered. When liver enzyme normalize, than give first line ATT and discard the toxic agent drug by trial.[19] Re exposure to the same drugs leads to recurrence of drug induced hepatitis.[20] According to ATS and BTS restart ATT one at a time. Restart ATT all the drugs simultaneously advice by WHO and IUAT. If there is second bout of hepatotoxicity then the ATT drugs are to be re introduced consequently.[20] Reintroduction without pyrazinamide showed safety of regimen.[21] Regimen without pyrazinamide was suitable to those individuals who were at risk of drug induced hepatitis; malnutrision HIV, low albumin and alcoholics.[20] NICE guidelines 2016 do not have clear guidance about liver function test in patients with active TB to detect drug induced hepatitis. They recommend full dose reintroduction of ATT in those patients who were interrupted due to drug induced hepatitis.

CONCLUSION

There is increased incidence of treatment failure of pulmonary tuberculosis after drug induced hepatitis. Liver function should be monitored during treatment. Patient and their relatives counseled for the treatment of pulmonary tuberculosis. Monitor risk factors old age, malnutrition, female gender, alcohol, concomitant infection with HCV, HBV and HIV. Regular monitoring of the treatment is helpful enhances its effectiveness. Early weeks to months are essential to monitor the hepatotoxicity. Recognition of more toxic drug is important and continue with remaining drugs, complications and mortality can be reduced.

Author's Contribution:

Concept & Design of Study:	Jeando Khan Daidano
Drafting:	Mujahid Chandio, Jeando Khan Daidano
Data Analysis:	Mujahid Chandio, Mukhtiar Abro
Revisiting Critically:	Mukhtiar Abro, Rafique Ahmed Memon, Jeando Khan Daidano
Final Approval of version:	Jeando Khan Daidano

Conflict of Interest: The study has no conflict of interest to declare by any author.

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